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Landiolol for heart rate control in patients with septic shock and persistent tachycardia. A multicenter randomized clinical trial (Landi-SEP)

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Abstract

Purpose: Excessive tachycardia in resuscitated septic shock patients can impair hemodynamics and worsen patient outcome. We investigated whether heart rate (HR) control can be achieved without increased vasopressor requirements using the titratable highly selective, ultra-short-acting β1-blocker landiolol.

Methods: This randomized, open-label, controlled trial was conducted at 20 sites in 7 European countries from 2018 to 2022 and investigated the efficacy and safety of landiolol in adult patients with septic shock and persistent tachycardia. Patients were randomly assigned to receive either landiolol along with standard treatment ($n=99$) or standard treatment alone ($n=101$). The combined primary endpoint was HR response (i.e., HR within the range of 80—94 beats per minute) and its maintenance without increasing vasopressor requirements during the first 24 h after treatment start. Key secondary endpoints were 28-day mortality and adverse events.

Results: Out of 196 included septic shock patients, 98 received standard treatment combined with landiolol and 98 standard treatment alone. A significantly larger proportion of patients met the combined primary endpoint in the landiolol group than in the control group (39.8% [39/98] vs. 23.5% [23/98]), with a between-group difference of 16.5% (95% confidence interval [CI]: 3.4–28.8%; $p=0.013$). There were no statistically significant differences between study groups in tested secondary outcomes and adverse events.

Conclusion: The ultra-short-acting beta-blocker landiolol was effective in reducing and maintaining HR without increasing vasopressor requirements after 24 h in patients with septic shock and persistent tachycardia. There were no differences in adverse events and clinical outcomes such as 28-day mortality vs. standard of care. The results of this

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study, in the context of previous trials, do not support a treatment strategy of stringent HR reduction (< 95 bpm) in an unselected septic shock population with persistent tachycardia. Further investigations are needed to identify septic shock patient phenotypes that benefit clinically from HR control.

Keywords: Landiolol, Ultra-short-acting beta-blocker, Sepsis, Septic shock, Persistent tachycardia, Heart rate control

Introduction

Septic shock-related inflammation results in hypovolemia and a reduction of cardiac output [1–3]. To maintain vital organ perfusion, massive sympathetic activation through the release of catecholamines is triggered leading to tachycardia, vasoconstriction, and increase in inotropism [4]. Current treatment guidelines [5, 6] recommend intravascular fluid administration and vasopressor therapy as the first step of hemodynamic management. However, in some patients, elevated heart rate (HR) persists, which may reflect sympathetic overstimulation [7–14]. Persistent tachycardia impairs preload and coronary perfusion and is associated with mortality and morbidity in a range of clinical conditions [15–18]. The threshold of 95 beats per minute (bpm) was reported as a predictive cut-off value to differentiate between survivors and non-survivors [19], while the range of 80−94 bpm is recognized as adequately balancing improved cardiac function and preserved systemic hemodynamics [9, 20]. These findings suggest that adequate HR control may improve the outcome of septic shock patients with tachycardia.

Beta1-selective beta-blockers, such as esmolol and landiolol, are considered suitable for the management of tachycardia in septic patients, as their administration resulted in improved stroke volume, lactate levels, a reduction of noradrenaline requirements, improvements in organ function, and survival rates [9, 20–23]. Due to their pharmacological properties, short-acting beta1-blockers in combination with vasopressors seem to be most appropriate approach to control HR during sepsis without systemic adverse effects [9, 20–32]. Other antiarrhythmic agents, such as ivabradine or amiodarone, showed HR reduction in clinical trials in septic shock patients but may lack the beneficial pleiotropic effects of beta-blockers, which include attenuating sympathetic overstimulation, increasing microcirculatory blood flow, blunting the inflammatory response, metabolic changes, and sepsis-associated coagulopathy [33, 34]. Beta-blockers were associated with superior clinical outcomes in a large retrospective study evaluating atrial fibrillation (AF) treatment in sepsis [35]. Non-selective beta-blockers are generally longer acting and may therefore be less suitable in the acute phase of sepsis [36]. The widespread use of beta-blockers is restrained due to possible induction of hypotension and bradycardia. High-quality data on the safety and efficacy of beta-blockade during septic shock are missing and recommendation on HR management in the current sepsis treatment guidelines remains limited. Landiolol has a shorter elimination half-life (4 min [37]) than esmolol (9 min [38]) and higher selectivity for beta1 receptors [4], resulting in lower negative inotropic effects [39–41] and reduced impact on blood pressure (BP) [42].

Take-home message

Titrated intravenous landiolol increases the proportion of septic shock patients with persistent tachycardia, who have a reduced and maintained heart rate without a vasopressor increase after 24h without differences in adverse events and clinical outcomes. These results, in the context of previous trials, do not support a treatment strategy of stringent heart rate reduction (<95 bpm) in an unselected septic shock population with persistent tachycardia. Notably, lower mortality was observed in patients with atrial fibrillation. Further research should aim to identify characteristics of patients who benefit from heart rate control and who do not.

Up to date, only two multicenter studies were conducted with landiolol in septic patients. In the J-Land 3S study conducted in Japan, the administration of landiolol resulted in significantly more patients with sepsis-related tachyarrhythmia achieving a target HR of 60–94 bpm at 24 h while showing comparable safety profile to the control group. The study also reported a reduction in 28-day mortality: 12% in the control group vs 20% in the landiolol group ($p = 0.22$) [43]. However, the most recent study conducted in the United Kingdom (UK) (STRESS-L) was terminated prematurely after the enrolment of 37% of the planned patients, because landiolol was unlikely to demonstrate benefit in improving organ function and there was a signal for possible harm [44]. These studies reported inconsistent findings on the benefit and safety of landiolol in tachycardia patients with septic shock [9, 43]. Therefore, there is an urgent need for additional studies to provide comprehensive data on the efficacy and safety of landiolol in septic shock patients with persistent tachycardia and vasopressor therapy.

We aimed to evaluate, whether the administration of landiolol in patients with septic shock and persistent tachycardia (HR ≥ 95 bpm) is effective in reducing and

maintaining HR, without increasing vasopressor requirements compared to standard treatment alone.

Methods

Ethics

The study was conducted in compliance with the Declaration of Helsinki and ICH Good Clinical Practice (GCP) guidelines. The study protocol [45] was approved by the relevant independent ethics committee at each participating center. Written informed consent was obtained from all patients or patient's legal representative(s) before any intervention. The final study protocol and the Statistical Analysis Plan (SAP) are available in the electronic supplementary material (ESM). An Independent Data Monitoring Committee regularly reviewed the trial data.

Trial design and objectives

The LANDI-SEP trial was a multicenter, randomized, open-label, controlled phase IV trial in intensive care unit (ICU) patients with septic shock and persistent tachycardia (HR ≥ 95 bpm). The study was conducted at 20 sites in 7 European countries. The primary objective of the trial was to compare an HR response and its maintenance thereof without an increase in vasopressor requirements within the first 24 h of treatment between landiolol and control groups. Further assessments of efficacy and safety in the two study groups were set as secondary objectives.

Patients

Eligible to the study were adult patients (> 18 years) in the ICU with septic shock as defined by the Sepsis-3 Criteria [46], with persistent tachycardia (HR ≥ 95 bpm) despite a hemodynamic optimization phase of at least 12 h but a maximum of 36 h in which they received treatment according to the Surviving Sepsis Campaign (SSC) guidelines [6]. Patients with any form of compensatory tachycardia, as determined by the Investigator, were not eligible. Selection criteria are fully stated in supplemental Table 2-Study protocol [45]. Patients were randomized in a 1:1 ratio to landiolol or control group according to the randomization list generated by the study statistician. The presence of AF in the hemodynamic optimization period was used as a stratification factor. Treatments were assigned to individual patients based on block stratified randomization to ensure random assignment to treatments and balanced distribution of both treatment arms within each stratum. The intervention was open label due to the absence of a specific study treatment in the control group.

Interventions

Landiolol group

In addition to standard treatment based on SSC guidelines [6], patients started continuous infusion of landiolol hydrochloride within 2 h after randomization at a starting dose of 1 µg/kg/min. In the titration phase (0–24 h), the dose was increased at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min at intervals of at least 20 min to reach a target HR of 80–94 bpm. After achievement of the target HR, landiolol was administered at any dose to maintain target HR until one the following events occurred: discontinuation of vasopressor infusion, death, serious adverse event (SAE) attributable to the study drug infusion, and patient's discharge from ICU or day 28. Landiolol was administered until discontinuation of vasopressors to maximise its potential beneficial effects on sympathetic overstimulation [47].

Control group

Patients received standard treatment according to the SSC guidelines [6], which was not targeted to HR control. End of treatment was defined as one the following events: discontinuation of vasopressor infusion, death, and patient discharge from the ICU or day 28. Patients were discontinued from the study if they received beta-blocker treatment.

Procedures

Hemodynamic data [HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP)] were documented hourly in the titration phase and every 12 h thereafter until end of treatment. Rate of vasopressor and inotrope infusion was recorded at every dose change. Detailed descriptions of the trial procedures are given in supplemental Table 3.

Study endpoints

Primary endpoint

The primary endpoint (PE) was a multi-component endpoint defined by achieving HR response (3 subsequent hourly HR values at 80–94 bpm or < 80 bpm and not clinically relevant), HR maintenance (defined as not recording 3 subsequent hourly HR values > 94 bpm or < 80 bpm after achievement of HR response), and no increase in vasopressor requirements during the first 24 h after treatment. Vasopressor response was defined as no increase of noradrenaline equivalent dose [48] at 24 h compared to the treatment start. HR values < 80 bpm were not deemed as response failure if the investigator considered the HR to be not clinically relevant (i.e., not assessed as relative bradycardia, without hemodynamic compromise). Individual endpoints, i.e., HR response (with or without maintenance) and vasopressors response, were also evaluated separately.

Secondary endpoints

Secondary endpoints included change in vasopressor requirements over the study period (dose and duration); 28-day/ICU mortality; duration of ICU/hospital stay; and Sequential Organ Failure Assessment (SOFA) score. The incidence rates of bradycardic episodes requiring intervention, adverse events (AEs), and SAEs were secondary safety endpoints.

Statistical analyses

Primary efficacy analysis

Absolute and relative frequencies of patients who achieved the PE were calculated. The comparison of study groups was conducted using a weighted Cochran–Mantel–Haenszel framework with two stratification factors: the presence of AF and site. The hypothesis that landiolol group is superior to control group in the proportion of patients who reached the PE was demonstrated if the lower limit of two-sided 95% confidence interval of difference pL–pC was above zero, where pL and pC are percentages of patients who reached the PE in landiolol and control groups, respectively. The PE was measured within 24 h after treatment initiation. Patients who died or were discontinued due to administration of beta-blockers during the first 24 h without reaching the PE were included in the analysis with the outcome that the PE was not reached.

Secondary efficacy and safety analyses

Secondary efficacy and safety analyses are fully described in the SAP (see electronic supplementary material).

Subgroup analyses

Subgroup analyses for the primary and secondary efficacy endpoints were defined post hoc for exploratory purposes and are specified in the SAP (see electronic supplementary material).

Results

Study participants

Between 24th February 2018 and 16th February 2022, we enrolled 196 patients (Fig. 1). Patient characteristics at baseline were similar in both study groups (Table 1). Landiolol doses and duration of administration are provided in supplemental Table 4.

Primary efficacy endpoint

In the landiolol group, 39.8% [39/98] of patients achieved the primary combined endpoint compared to 23.5% [23/98] in the control group, with a difference between the interventions of 16.5% (95% confidence interval [CI] 3.4–28.8%; $p=0.013$). 75.5% [74/98] patients in the landiolol group reached target HR when compared to 42.9% [42/98] in the control group, with a difference between the groups of 33% (95% CI 19.4–44.9%; $p=<0.001$). The difference between the vasopressors response rates was not statistically significant between study groups (Table 2).

Main secondary endpoints

Other efficacy measures

There were no statistically significant differences in 28-day and ICU mortalities between landiolol and control groups. Cox proportional hazards model from day 0 to day 28 showed no difference in survival between the study groups (HR 1.35 [95% CI 0.85–2.13], $p=0.20$). No difference was observed between study groups for the durations of ICU stay (HR 1.17 [95% CI 0.70–1.94]; $p=0.55$) and hospital stay (HR 0.80 [95% CI 0.41–1.54], $p=0.50$) for patients alive on day 28. The secondary endpoints are summarized in Table 3. The duration of vasopressor administration was similar between study groups, with a mean (standard deviation, SD) duration of 5.64 (7.16) and 5.08 (5.20) days for the landiolol and control group, respectively. The mean (SD) total dose of noradrenaline over the treatment period was 194.6 (287.7) and 138.46 (158.7) mg for landiolol and control group, respectively. Inotropic agents were used in nine patients in the landiolol group with a mean (SD) duration of 3.95 (3.78) days and in nine patients in the control group with a mean (SD) duration of 1.32 (1.13) days. The average and total doses of vasopressors and inotropic agents administered in the study are summarized in supplemental Tables 5 and 6, respectively. Mean profiles of vasopressor doses administered during the titration phase and the study are displayed in Fig. 2e and f, respectively. SOFA scores were analysed descriptively for the visits before the end of study treatment and were comparable between study groups (supplemental Table 7). The levels of arterial lactate were comparable over the first 4 days of the study between the study groups (supplemental Table 8). While mean (SD) values for HR [bpm] were not different at baseline between the landiolol group [116 (14.86)], and control group [114.2 (13.50)], statistically significant differences were observed at 1 h after treatment start [101.8 (13.49) vs 111.3 (15.35), $p<0.001$]. HR remained lower in the landiolol group compared to the control group at 24 h [90.2 (15.77) vs 101 (22.52), $p<0.001$] and on day 2 [84.3 (13.64) vs 93.4 (17.03), $p=0.002$] after treatment start. Thereafter, the HR in patients in the control group also stabilized and there was no significant difference in HR between the groups after day 2 (Fig. 2a, b). The values for MAP, SAP,

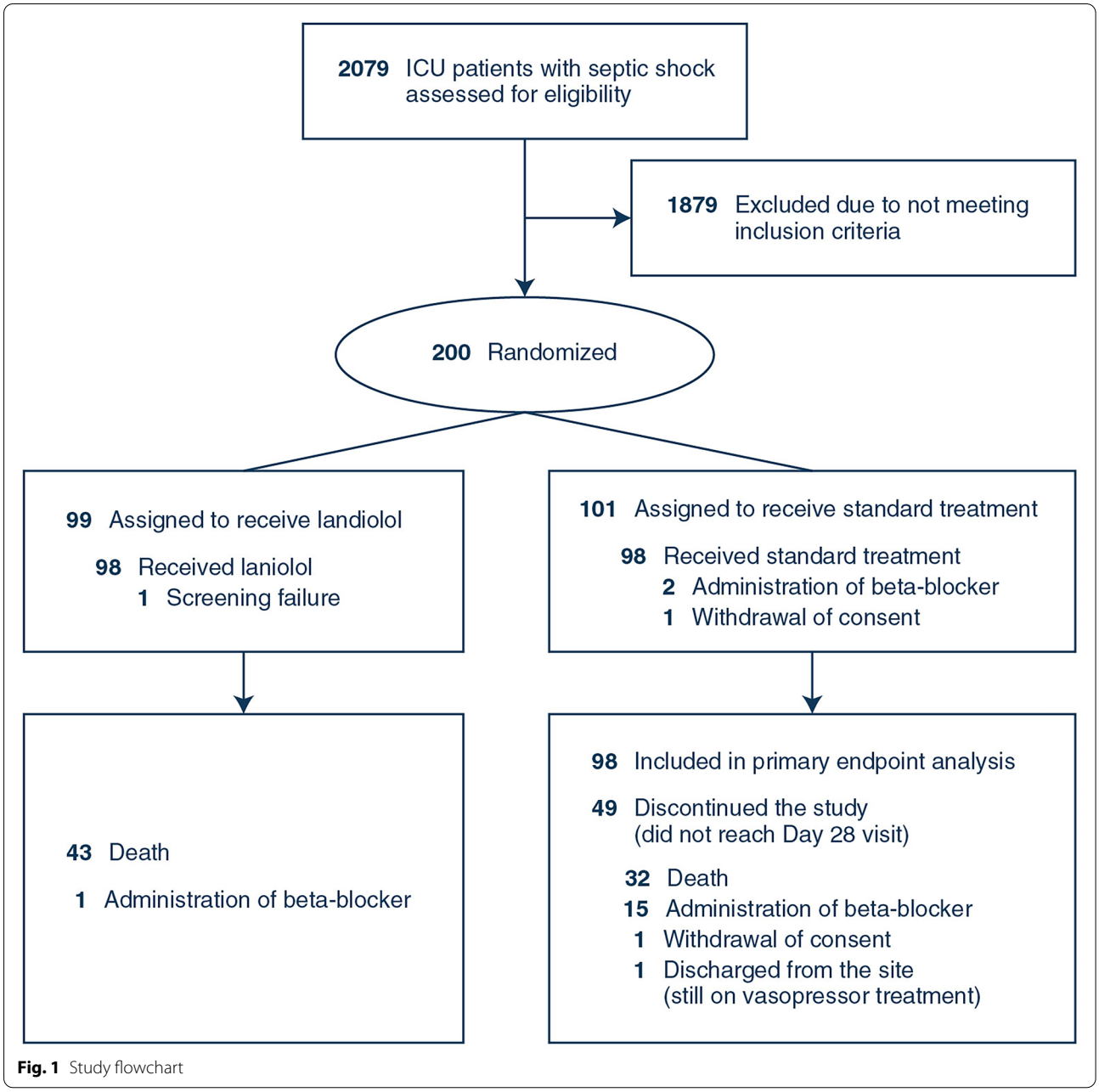
2079 ICU patients with septic shock assessed for eligibility
1879 Excluded due to not meeting inclusion criteria
200 Randomized
99 Assigned to receive landiolol
98 Received laniolol
1 Screening failure
101 Assigned to receive standard treatment
98 Received standard treatment
2 Administration of beta-blocker
1 Withdrawal of consent
43 Death
1 Administration of beta-blocker
98 Included in primary endpoint analysis
49 Discontinued the study (did not reach Day 28 visit)
32 Death
15 Administration of beta-blocker
1 Withdrawal of consent
1 Discharged from the site (still on vasopressor treatment)

Fig. 1 Study flowchart

and DAP were comparable between the study groups over the study period (Fig. 2c, d).

Safety analyses

A total of 166 AEs were reported in 66/98 (67.3%) patients in the landiolol group and 159 AEs in 65/98 (66.3%) patients in the control group (supplemental Table 9). 74 SAEs were reported in 54/98 (55.1%) patients in the landiolol group and 68 SAEs in 52/98 (53.1%) patients in the control group (supplemental Table 10). The most frequent AEs related to landiolol were hypotension in 5 (5.1%) and bradycardia in 2 (2%) patients. SAEs related to landiolol were low cardiac output syndrome (reduced ejection fraction and hypotension) and hypotension in 1 (1%) patient, respectively. Landiolol-related events resolved with dose reduction, dose interruption, or discontinuation of landiolol. No fatal event was considered related to landiolol treatment. Five bradycardic episodes requiring intervention occurred in four patients in the landiolol group, and three episodes in two patients were related to landiolol. All events resolved after landiolol discontinuation or

Table 1 Baseline characteristics of the study participants

Variable, statistics	Landiolol group ($n=98$)	Control group ($n=98$)
Age, mean (SD), years	64.4 (12.5)	65.2 (15.06)
Gender, n (%)		
Female	35 (36)	43 (44)
Male	63 (64)	55 (56)
Atrial fibrillation[a], n (%)		
No	72 (73)	74 (76)
Yes	26 (27)	24 (24)
APACHE II score, mean (SD)	24.9 (8)	23.6 (8.6)
SOFA score, mean (SD)	12.6 (3.54)	12.1 (2.83)
Noradrenaline equivalent dose, mean (SD)	0.51 (0.51)	0.52 (0.54)
MAP, mean (SD), mmHg	78.6 (10.2)	79 (10.36)
SAP, mean (SD), mmHg	119.5 (17.02)	119.6 (16.62)
DAP, mean (SD), mmHg	59.7 (9.49)	60.1 (10.14)
HR, mean (SD), bpm	116 (14.86)	114.2 (13.5)
Cardiac rhythm[b], n (%)		
Missing	8	7
Arrhythmia	24 (27)	20 (22)
Sinus rhythm	66 (73)	71 (78)
Time since septic shock diagnosis, mean (SD), h	23.95 (10.54)	25.34 (7.68)
Renal replacement therapy, n (%)	24 (24)	22 (22)
Mechanical ventilation, n (%)	83 (85)	78 (80)
Left ventricular ejection fraction[c], mean (SD), %	55.2 (13.39)	55.1 (12.46)
Velocity time integral[d], mean (SD), cm	19.4 (5.37)	19.3 (5)
Arterial lactate level, mean (SD), mmol/L	4 (3.3)	3.9 (3.6)
Arterial pH, mean (SD)	7.33 (0.11)	7.35 (0.09)
Fluid balance, mean (SD), ml/day	4719 (3842.2)	4126 (3606.4)
Respiratory infection, n (%)	42 (43)	44 (45)
Abdominal infection, n (%)	40 (41)	30 (31)
Urinary tract infection, n (%)	16 (16)	11 (11)
Surgical infection, n (%)	4 (4)	9 (9)
Other infection, n (%)	15 (15)	18 (18)

APACHE II score Acute Physiology and Chronic Health Evaluation score, *SOFA* score, Sequential Organ Failure Assessment score, *MAP* Mean Arterial Pressure, *SAP* Systolic Arterial Pressure, *DAP* Diastolic Arterial Pressure, *HR* Heart Rate, *BMI* Body Mass Index, *SD* Standard Deviation

[a] Presence of atrial fibrillation in the haemodynamic optimization period

[b] Cardiac rhythm assessment at baseline

[c] $N=66$

[d] N (Landiolol group) = 54, N (Control group) = 56

dose reduction. New-onset arrhythmias were observed in 13.3% [13/98] and 17.3% [17/98] patients in the landiolol and control groups, respectively, with no significant difference between the groups ($p=0.55$). Summary of safety analyses is provided in supplemental Table 11.

Additional and subgroup analyses

Subgroup analyses

In univariate, unadjusted analyses (supplemental Fig. 1), the percentage of patients achieving the combined PE was greater in the landiolol group in all subgroups of patients, except from patients affected with coronavirus disease 2019 (COVID-19), where sample size was small. Similar results as for the whole population were observed in the subgroups of patients with AF (supplemental Table 12) and in patients with LVEF > 65% at baseline (supplemental Table 13).

Discussion

The main finding of this study is that in septic shock patients with persistent tachycardia, the titrated highly selective, ultra-short-acting beta1-blocker landiolol

Table 2 Primary efficacy analyses

Response	Landiolol group ($n=98$)	Control group ($n=98$)	Overall ($n=196$)	Effect estimate (95% CI)	*P* value
Primary response (multi-component)[a], n (%)	39 (39.8)	23 (23.5)	62 (31.6)	MD, 16.5% (3.4–28.8%)	0.01
Components of primary endpoint					
HR response (target HR reached and maintained)[b], n (%)	57 (58.2)	29 (29.6)	86 (43.9)	MD, 29% (15.1–41.3%)	< 0.001
HR response (target HR reached, not necessarily maintained)[c], n (%)	74 (75.5)	42 (42.9)	116 (59.2)	MD, 33% (19.4–44.9%)	< 0.001
Vasopressors response[d], n (%)	56 (57.1)	65 (66.3)	121 (61.7)	MD, − 9.2% (− 22 to 4.4%)	0.19

HR heart rate, *CI* confidence interval, *MD* mean difference

[a] Primary response definition: achieving HR response (3 subsequent hourly HR values at 80 – 94 bpm or < 80 bpm and not clinically significant), HR maintenance (defined as not recording 3 subsequent hourly HR values > 94 bpm or < 80 bpm after achievement of HR response), and no increase in vasopressor requirements during the first 24 h after treatment

[b] HR response definition (target HR reached and maintained): 3 subsequent hourly HR values at 80 – 94 bpm or < 80 bpm and not clinically significant), HR maintenance (defined as not recording 3 subsequent hourly HR values > 94 bpm or < 80 bpm after achievement of HR response), and no increase in vasopressor requirements during the first 24 h after treatment

[c] HR response definition (target HR reached, not necessarily maintained): 3 subsequent hourly HR values at 80–94 bpm or < 80 bpm and not clinically significant during the first 24 h after treatment

[d] Vasopressor response definition: no increase of noradrenaline equivalent dose at 24 h compared to the treatment start

Table 3 Secondary efficacy analyses

Response	Landiolol group ($n=98$)	Control group ($n=98$)	Overall	Effect estimate (95% CI)	*P* value
28-day mortality, n (%)[a]	43 (43.9)	39 (40.2)	82 (42.1)	MD, 3.8% (− 9.9 to 17.3%)	0.60
ICU mortality, n (%)[b]	43 (43.9)	33 (34)	76 (39)	MD, 9.9% (− 3.8 to 23%)	0.16
Duration of ICU stay for patients alive on day 28, median (95% CI), days	14 (10.2–15.3)	13.9 (10.2–20.4)	–	HR, 1.17 (0.70–1.94)	0.55
Duration of hospital stay for patients alive on day 28	–	–	–	HR, 0.80 (0.41–1.54)	0.50

CI confidence interval, *HR* hazard ratio, *ICU* intensive care unit, *MD* mean difference, *SD* standard deviation

[a] *N* (Landiolol group) = 98, *N* (Control group) = 97

represents an effective approach to reduce and control HR in patients requiring vasopressors. Notably, compared to the control group, a higher proportion of patients treated with landiolol reached the combined PE, i.e., HR reduction and maintenance without an increase in noradrenaline doses after 24 h, compared to the control group. The result was primarily based on the difference between the two groups in achieving and maintaining target HR, while vasopressor doses tended to be higher in the landiolol group. This was achieved despite 35.7% (35/98) patients in the control group receiving antiarrhythmic medication during the first 24 h. Landiolol administration led to prompt HR control and consistent differences in HR from baseline values compared to the control group within the first 24 h, while no significant impact on the blood pressure (BP) was observed. Compared to the control group, heart rate reduction was statistically significant during the first two days of landiolol treatment. In other words, patients in the control group suffered from higher HR for 48 h longer than landiolol treated patients. Following the study rationale, these findings support the reduction of adrenergic stress by landiolol. Primary response was consistent throughout all predefined and post hoc subgroups, except for patients with COVID-19.

Our study represents the largest population in currently published multicentre randomized trials on beta-blockers in septic shock patients. Baseline characteristics are representative of patients with septic shock and persistent tachycardia admitted to ICU. Patients with various primary locations of infection, age, gender, comorbidities, and overall health status allow for generalisability of trial findings. Illness severity was evidenced by the high APACHE II scores, noradrenaline equivalent doses, and arterial lactate values at baseline (Table 1). Landiolol administration was not associated with a reduction of vasopressor requirements or an improvement in survival compared to the control group. The 28-day mortality rate

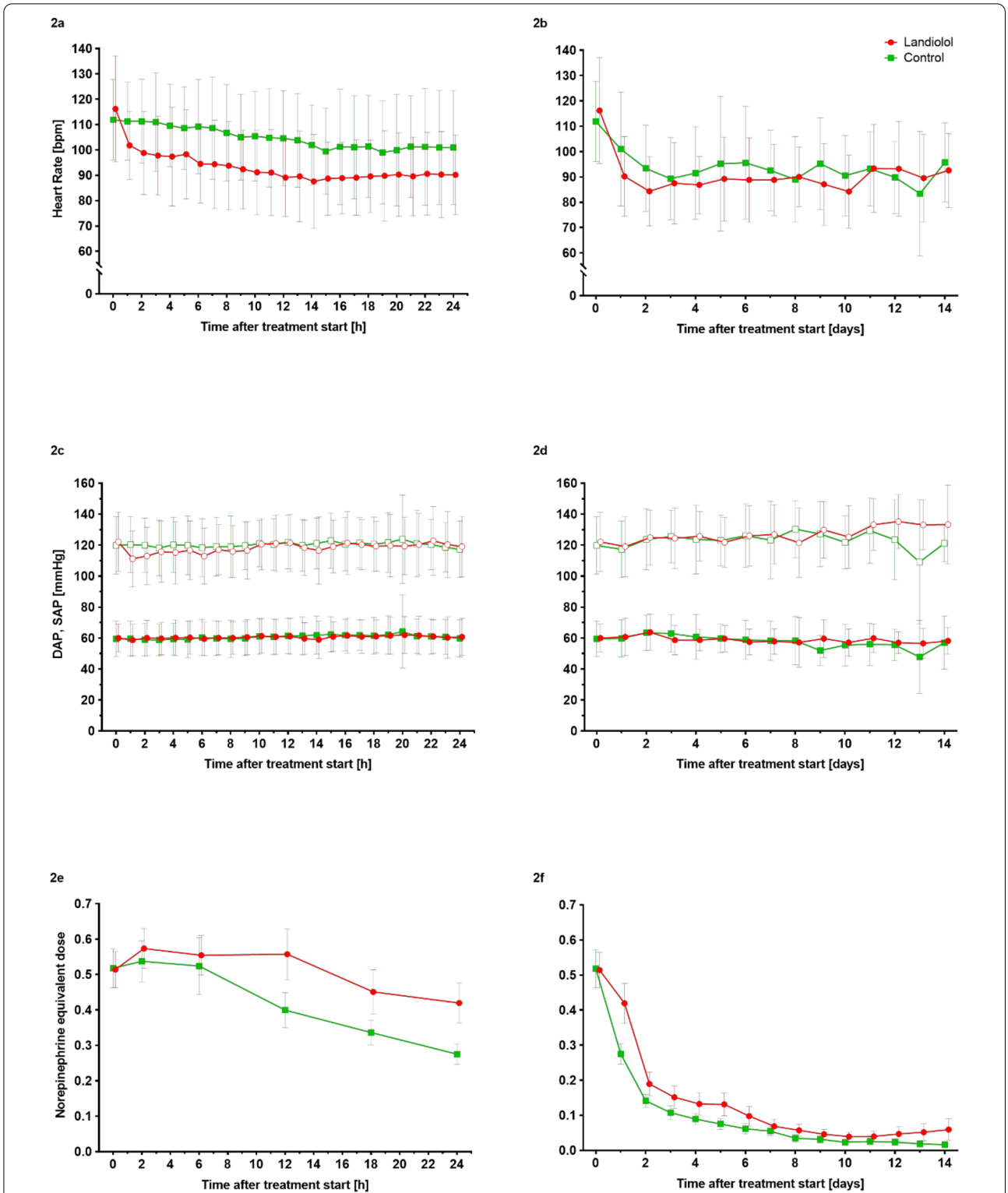

Fig. 2 Mean (SD) profiles of HR in the titration phase (**a**)/during the study up to day 14 (**b**), Mean (SD) profiles of blood pressure in the titration phase (**c**)/during the Study up to day 14 (**d**) and Mean (SE) norepinephrine equivalent dose during the titration phase (**e**)/during the study up to day 14 (**f**). *bpm* beats per minute, *DAP* diastolic arterial pressure, *SAP* systolic arterial pressure, *mmHg* millimetre of mercury

in our study for patients treated with landiolol (43.9%) was comparable to the STRESS-L study (37.1%) [44]. The latter study was stopped prematurely, because there was a signal of possible harm due to the low 28-day mortality rate of 25.4% in the control group (vs. 40% in the present study). While the representativeness of the control group of the STRESS-L study was brought into question [49], the mortality rates for landiolol reported in our and the STRESS-L study are in line with published data for general patients with septic shock [50, 51]. Notably, in a cohort of septic and septic shock patients, the J-Land 3S study showed a trend for lower mortality in patients treated with landiolol vs. standard of care [43, 52]. In our study, no differences in clinical outcomes such as 28-day mortality, duration of ICU/hospital stay or time of survival were shown between landiolol and standard of care even though comparable effects in HR reduction and maintenance of BP were observed under comparable landiolol doses. Importantly, the sample size of our study was not primarily powered for robust evaluations of these endpoints. However, several factors discussed below could have contributed to these results.

The protocol did not require detailed hemodynamic monitoring or advanced echocardiography. The lack of the insight into the hemodynamic profiles of individual patients could have led to the enrolment of patients with tachycardia, who did not benefit from HR reduction. Due to the lack of universally accepted criteria for the definition of non-compensatory tachycardia, methods of identification of such patients were at the investigator's discretion. Observed decreases in BP in the early phase of landiolol treatment and increases in vasopressor doses suggest that some patients with compensatory tachycardia were indeed included. The lack of cardiac output measurement and orientation on achieving target HR prevented investigators to individualise treatment targets (e.g., to titrate landiolol to optimise cardiac output). While the incidence of hypotension was low in both study groups, we hypothesize that due to the adherence to the HR goal, investigators were more likely to increase vasopressor dose in these patients than to reduce landiolol dose. The stringent approach of targeting a fixed HR does not take full advantage of the titratability of an ultra-short-acting beta-blocker like landiolol and may have been too aggressive in patients with higher HR. The protocol allowed the enrolment of patients with other than sinus rhythm or pre-admission beta-blocker therapy, which might have also influenced the individual responses to treatment [53]. Post hoc subgroup analysis showed higher mortality risk for the landiolol group (47.2% [34/72]) compared to the control group (39.7% [29/73]) in patients with sinus tachycardia, while the opposite was observed in patients with AF (34.6% [9/26] vs 41.7% [10/24]) (supplemental Table 12). This finding, albeit not statistically significant, could also reflect the benefit of improved diastolic filling time in patients with the absence of the atrial kick. The use of inotropic agents was rare in our study with only nine patients in each group receiving dobutamine, levosimendan, or milrinone. In the Japanese study, around 40% of patients were administered dobutamine and phosphodiesterase III inhibitors in the landiolol group [52]. In the single-center study by Morelli et al. that reported a significant decrease in 28-day mortality using esmolol in a similar patient population, 49.4% of patients received levosimendan [9].

Safety was comparable between the landiolol and control group with respect to AE and SAE rates. There was no difference in the incidence of new-onset arrhythmia between groups, but this may have been influenced by the wide use of antiarrhythmic medication in the control group (supplemental Table 14). Hypotension and bradycardia related to landiolol administration were rare with only 5, respectively, 3 patients experiencing such events. All events were resolved after prompt intervention by the treating physician.

Our results in the context of previous trials with beta-blockers in septic shock suggest that the enrolled population comprises patients who could clinically benefit from HR control, but also those in whom tachycardia should not be specifically treated. The goal of future research is to identify those subgroups, in which personalised treatment with a titratable rapidly acting beta-blocker landiolol can be a powerful tool. For example, the subgroup of patients with a hyperdynamic heart at baseline (LVEF > 65%) showed numerically lower mortality at day 28 compared to control in our study (supplemental Table 13). A randomized-controlled trial investigating the use of landiolol in this patient population with overall increased mortality is currently ongoing (NCT04748796). Future research might focus on the group of patients with AF, as demonstrated in the respective subgroup of this study (supplemental Table 12), as well as patients with preexisting chronic beta-blocker therapy, as suggested by the data of Fuchs et al. [53]. To identify these specific conditions, more detailed monitoring of hemodynamics at baseline and during the treatment in future trials seems paramount, and so is a more stringent exclusion of patients, who might not benefit. While correct identification of patients with non-compensatory tachycardia remains challenging, a recent post hoc analysis by Morelli et al. identified the systolic and dicrotic pressure difference as a potential discriminator for the origin of the tachycardia [54].

Limitations

Potential limitations of the trial include the open-label design and the lack of requirement for more detailed hemodynamic monitoring, which may have led to enrolment of patients with a compensatory sinus tachycardia who did not benefit from HR reduction. Also, the evaluation of the effect of landiolol on cardiac function remains limited. Our study was designed to explore hemodynamic responses, but it was not powered to investigate mortality or other robust patient-centred outcomes. The primary endpoint evaluated in our study has not been validated as a surrogate marker for clinical outcomes. Furthermore, study centres varied in their previous experience with intravenous beta-blocker use in this patient population. The study was recruiting throughout the initial phase of the COVID-19 pandemic, which might have had an impact on patient care especially in the landiolol group that contrary to the control group required additional attention of doctors and nurses. More patients with COVID-19 were included in the landiolol group and this was the only subgroup in which primary outcome tended to be worse with landiolol treatment.

Conclusion

Titrated administration of the highly selective, ultra-short-acting beta1-blocker landiolol in patients with septic shock and persistent tachycardia was effective in reducing and maintaining HR without increasing vasopressor requirements within the first 24 h. There were no differences in adverse events and clinical outcomes, such as 28-day mortality, duration of ICU/hospital stay or time of survival, between patients treated with landiolol vs. sole standard of care. These results, in the context of previous trials, do not support a treatment strategy of stringent HR reduction (<95 bpm) in an unselected septic shock population with persistent tachycardia. Subgroup analysis showed a trend for lower mortality in patients with atrial fibrillation but reverse trend for higher mortality in patients with sinus tachycardia. Further investigations are needed to identify septic shock patient phenotypes that benefit clinically from HR control.

Supplementary Information

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Data availability statement
The data that support the findings of this study are openly available in EU Clinical Trials Register at https://www.clinicaltrialsregister.eu/, EudraCT Number: 2017-002138-22.

Declarations

Conflicts of interest
All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. MU, JS, CK, KK, NKB are employees of AOP Orphan Pharmaceuticals GmbH. GK is a Board Director of AOP Health International Management AG.

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